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Usefulness of a Low-Dose Intravenous Immunoglobulin Regimen for the Treatment of Thrombocytopenia Associated With AIDS

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Infection with the human immunodeficiency virus (HIV) frequently is complicated with thrombocytopenia (HIV-Thr) during all stages of the infection. The treatments for autoimmune thrombocytopenic purpura (ITP) are used in HIV-Thr; however, their effects upon the immune status of patients with acquired immunodeficiency syndrome (AIDS) are unknown. Intravenous immunoglobulin (IVIg) is used in patients with ITP and HIV-Thr; however, its usefulness in thrombocytopenic AIDS patients has not been directly addressed. We used a low-dose IVIg regimen (0.04 g/kg per week during five weeks) for the treatment of HIV-Thr complicating AIDS. Thirteen patients received IVIg. We observed a response to IVIg in 13 patients by the end of week one and in 10 patients by the end of week five. Long-term response, evaluated three months after stopping IVIg, was present in four cases. IVIg was well tolerated and no opportunistic infections were observed during the study period. Compared with previous reports, we used 10% of the previously proposed dosage with an important decrease in the cost of treatment. Our results suggest that this low-dose IVIg regimen is a highly effective, nonexpensive alternative in treating HIV-Thr in AIDS. If sustained responses can be obtained with a similar low-dose maintenance regimen, IVIg may be the first choice for the treatment of HIV-Thr in AIDS patients. Am. J. Hematol. 59:127–132, 1998. © 1998 Wiley-Liss, Inc.

Key words: HIV; thrombocytopenia; intravenous immunoglobulin

INTRODUCTION

The association of human immunodeficiency virus (HIV) infection and thrombocytopenia (HIV-Thr) was first described in 1982 [1]. Today, HIV-Thr is recognized as a major hematologic complication of HIV infection affecting homosexual men [1,2], drug addicts [3], and patients with hemophilia [4]. HIV-Thr complicates 20% to 55% of patients with full-blown acquired immunodeficiency syndrome (AIDS) [5,6]. Whereas possible etiologies of HIV-Thr include platelet consumption associated with infection or hypersplenism and bone marrow failure, most cases appear similar to ''classical'' immune thrombocytopenic purpura (ITP).

The management of HIV-Thr is problematic. Although useful in some cases, steroids and splenectomy, the two most common treatments for ITP [7,8] are not completely desirable for asymptomatic HIV+ or AIDS patients. It has been demonstrated that the use of steroids increases the risk of Kaposi's sarcoma [9,10]. Although not completely demonstrated, concerns about splenectomy and the increase in the HIV-related immunological disturbances exist [11,12]; therefore, it should be considered as a therapeutic alternative only after all medical treatments have failed [13]. Zidovudine is now considered the first choice of treatment for HIV-Thr [13,14–18]; however, sometimes it is ineffective in AIDS patients. Therefore, evaluation of other therapies is warranted.

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Intravenous immunoglobulin (IVIg) is an alternative approach in patients with ITP [19,20]. Since the initial report about the use of IVIg for the treatment of HIV-Thr [21], a large body of information has been recorded demonstrating the usefulness of this drug in treating HIV-Thr [22–24]. However, except for a few cases described in some reports, there have not been studies specifically designed to determine the efficacy of IVIg for HIV-Thr in patients with full-blown AIDS.

Because of the high incidence of HIV-Thr among our AIDS patients and because of the lack of response to conventional therapy, we designed this study to evaluate the usefulness of a weekly low-dose IVIg regimen for the treatment of HIV-Thr in patients who are in the last stage of HIV infection.

PATIENTS AND METHODS

Patients

Only patients fulfilling the criteria for having AIDS [25] were enrolled in this study. We included adult patients of both sexes, with or without bleeding complications when IVIg therapy was started. None had received IVIg and with the exception of zidovudine, all other medication for HIV-Thr was discontinued for at least three weeks before starting IVIg. At our hospital, all AIDS patients receive zidovudine (500 mg/day), dideoxycitidine (2.25 mg/day), and a prophylactic treatment with sulphamethoxazole-trimethoprim (one double-strength tablet/day), isoniazide (300 mg/day), and folic acid supplement (5 mg/day). Any patient receiving platelet transfusions during the study was excluded.

An enzyme-linked immunosorbent assay and confirmation by Western blot analysis were used to detect antibodies to HIV. The diagnosis of HIV-Thr was made in the presence of severe thrombocytopenia (platelet count (PC) $< 50 \times 10^9$/l) and with normal or increased numbers of megakaryocytes in the bone marrow [26,27]. HIV-Thr was considered chronic when diagnosed six or more months before entering the study, otherwise it was categorized as acute [26]. Patients could have neither neoplasia, including Kaposi's sarcoma and lymphoma, nor splenomegaly. Other contributory causes of peripheral thrombocytopenia, such as thrombotic thrombocytopenic purpura (excluded by the clinical picture and normal peripheral blood smears), disseminated intravascular coagulation (excluded by a normal partial thromboplastin time and prothrombin time tests as well as normal levels of D-dimer), infectious systemic diseases, and liver disease (excluded on the basis of normal prothrombin time test and transaminases levels before treatment and at least once during the study period), were also ruled out.

Study Design

The IVIg preparation used (Sandoglobulina, a generous gift of Sandoz México) was given as a continuous IV infusion through a peripheral catheter at a dose of 0.04 g/kg per week for five consecutive weeks. Patients always received IVIg therapy on an out-patient basis.

Our response criteria were: 1. Complete response (CR): PC $> 100 \times 10^9$/l without bleeding complications; 2. Partial response (PR): PC $> 50 \times 10^9$/l with at least a two-fold increase of the initial PC in the absence of bleeding manifestations and; 3. No response: failure to increase the PC above 50×10^9/l. Patients were evaluated every week after starting IVIg (immediate response, IR), as well as three months after the end of the treatment (long-term response, LTR). We also recorded the hematological values before, during, and at the end of treatment. Lastly, we recorded the occurrence of infectious diseases during and after IVIg, and the side effects produced by the drug. Written consent was obtained from each patient before entering the study. The project was approved by the Ethics Committee of the Hospital General Regional Gabriel Mancera.

Statistical Analysis

The statistical analysis was performed using SigmaStat 2.0 statistical software (Jandel Corporation, San Rafael, CA). To compare the differences between the initial PC and the PC from successive weeks, we used a Kruskal-Wallis one-way analysis of variance on ranks test. We performed a logistic regression analysis in order to determine which variables affected the response to IVIg including time since AIDS diagnosis, age, evolution time of HIV-Thr, and hematological values. Differences were considered significant when P was less than 0.05.

RESULTS

From January to July of 1996, we studied 148 AIDS patients with HIV-Thr; however, only 13 fulfilled the inclusion criteria for this study. The general characteristics of these 13 patients are shown in Table I. All were male homosexual patients with a mean age of 31 years (ranges, 21 to 61 years). Mean evolution time of AIDS at the moment of HIV-Thr presentation was 10 months (ranges, 1 to 20). Acute and chronic thrombocytopenia were present in eight and five cases, respectively, and for the entire group the mean duration of HIV-Thr was six months (ranges, three to 10). Before entering the study, each patient had received other medical therapies for HIV-Thr: Prednisone ($n = 13$); ascorbic acid ($n = 6$); and danazol ($n = 4$). None had been splenectomized. Six cases had a history of bleeding complications related to HIV-Thr similar to ITP: epistaxis, purpura, gingival bleeding, and petechiae. Two patients (cases six and nine) had bleeding at the time of starting IVIg. Both had severe epistaxis that required nasal packing as well as platelet transfusions. We started IVIg because, despite these interventions, bleeding persisted.

TABLE I. General Characteristics of 13 Patients With HIV-Thr*

Patient (n)	Age (years)	AIDS evolution time (months)	HIV-Thr evolution time (months)	Bleeding history	Hb g/dl	WBC $\times 10^9$/l	PMNs $\times 10^9$/l	CD4 $\times 10^9$/l
1	61	10	3	No	8.7	1.6	1.0	181
2	29	7	6	Yes	12.5	0.9	0.4	52
3	28	13	8	Yes	14.5	4.4	2.9	156
4	30	8	8	Yes	9.8	3.1	0.9	165
5	33	19	4	No	12.1	1.7	0.6	74
6	21	1	6	Yes	4.0	1.1	0.4	121
7	32	16	5	No	11.3	2.4	1.3	123
8	26	10	7	No	12.3	1.9	0.8	123
9	31	8	3	Yes	7.3	3.4	2.1	86
10	33	6	5	No	10.2	2.8	1.4	88
11	32	20	4	No	14.3	4.5	1.7	95
12	34	20	10	Yes	13.3	1.0	0.2	150
13	31	14	7	No	12.9	2.5	1.1	135

*HIV-Thr, thrombocytopenia associated with human immunodeficiency virus infection; Hb, hemoglobin; WBC, white blood cell; PMNs, neutrophil counts.

Bone marrow aspiration was performed in all the patients and was normocellular or hypocellular in nine of four cases, respectively. Despite some minimal myelodysplastic changes, myeloid and erythroid progenitors were essentially normal. Megakaryocyte counts were normal or increased in all the samples; however, some degree of dysplasia was found in seven patients (basically, denuded and small megakaryocytes).

The entire study group completed the protocol treatment at full dose. We did not record hemorrhagic episodes during the IVIg infusion period. There were no significant changes in white blood cell (WBC), neutrophil, or total CD4 blood counts. Interestingly, one patient's hemoglobin (Hb) increased after starting IVIg (case 1). Because he had chronic anemia that was unresponsive to other treatments and because of the presence of giant normoblasts in the bone marrow, we believe that this individual likely had an autoimmune hemolytic anemia secondary to parvovirus B19 which responded to IVIg. For the rest of the group Hb remained unchanged. Transaminase levels were normal in each patient during the week before IVIg infusion and at least once while receiving the medication. PC before and during the five-week period of treatment as well as three months after termination of therapy are shown in Table II. For the two cases with bleeding at entry, hemorrhage stopped during the first six hr after IVIg. After one week, 11 patients achieved a CR (five of them with normal PC), and two reached PR. Although by the second week only four patients maintained CR, the entire group still maintained a response. By the third week, two patients became refractory to IVIg, and at the end of the treatment, only 10 patients had an IR. LTR was seen in five cases (38%), with three CR and two PR. One patient (case 12) bled four weeks after finishing IVIg (upper gastrointestinal bleeding). The logistic regression analysis showed that, except for IVIg treatment ($P < 0.0001$), any other variable analyzed significantly affected the response in the patients.

After 65 IVIg infusions, there were no complaints related to IVIg. We did not observe opportunistic infections from the beginning of the study up to the eighth week after stopping IVIg. Twelve weeks after finishing IVIg, all the patients were still alive, but three infectious episodes were recorded: two pneumonic events and one collangitis episode.

DISCUSSION

HIV-Thr is a major problem in HIV infection. Our facility is not an exception; in the last 5 years, of 643 AIDS patients, 311 (48%) had at least one episode of HIV-Thr (mild HIV-Thr, 68%; moderate, 23%; and severe, 9%). In agreement with previous reports, our patients with moderate and severe HIV-Thr had 13% of major thrombocytopenia-related hemorrhagic events [5,6,27].

HIV-Thr has sporadic spontaneous remissions and bleeding complications similar to ITP. For example, it has been reported that as high as 18% of cases with HIV-Thr undergo spontaneous remissions [2]. It is recommended that patients with mild HIV-Thr or without clinical bleeding should not receive treatment; however, the incidence of fatal bleeding in severe ITP is 5% [28], and 8% of cases with HIV-Thr have a hemorrhagic event [27]. Moreover, therapy is sometimes mandatory: patients with hemophilia or acute bleeding [29], emergency surgery, etc. Despite these facts, therapy for ITP is not fully applied to HIV-Thr because of its immunosuppressive effect on HIV+ patients, especially on those with AIDS. The possible contribution of prednisone to the development of AIDS is still unclear [12]. Splenectomy

TABLE II. PCs at the Start and During IVIg Treatment in 13 Patients with HIV-Thr†

n	Patient PC before IVIg ($\times 10^9$/l)	PC during IVIg infusion (weeks) ($\times 10^9$/l)					PC three months after IVIg ($\times 10^9$/l)
		1	2	3	4	5	
1	27	312	72	63	65	71	102
2	9	102	94	64	73	60	18
3	39	93	86	81	52	71	34
4	23	100	89	84	96	63	58
5	42	234	133	90	120	105	42
6	7	137	90	2	9	17	22
7	33	102	97	72	66	70	161
8	39	177	123	121	98	70	16
9	21	135	138	127	130	132	127
10	11	99	89	76	95	81	45
11	18	122	133	76	85	90	39
12	44	178	96	44	63	56	26
13	27	156	97	102	123	87	94
m	26	149*	102*	77*	82*	74*	60**
SD	12.7	63.1	21.3	32.1	33.3	25.3	46.1
CR (n/%)		11/85	4/31	3/23	3/23	2/15	3/23
RP (n/%)		2/15	9/69	8/62	7/54	8/62	1/8
F (n/%)		—	—	2/15	3/23	3/23	9/69

†PCs, platelet counts; HIV-Thr, thrombocytopenia associated with HIV infection; IVIg, intravenous immunoglobin; SD, standard deviation; CR, complete remission; PR, partial remission; F, failures.
*$P < 0.0001$ when compared vs. PC before IVIg.
**$P = 0.035$ when compared vs. PC before IVIg.

is useful [4,30], but it has been suggested that it may increase the risk of developing AIDS [31,32], and in AIDS cases with multiple metabolic or infectious complications or poor general performance, a nonemergency surgery may be an unacceptable high-risk procedure. Our experience with medical treatments has not been good: the response rate to prednisone is 30%. Zidovudine, the best treatment for HIV-Thr in AIDS-free cases [14], induces <15% responses in our patients. On this basis, we decided to explore the utility of IVIg.

To evaluate our results we chose the criteria proposing PR not only as an increase > 50 × 10^9/l in the PC but also raising the initial PC at least twice (raising the PC > 50 × 10^9/l may be properly called PR for an initial PC < 20 × 10^9/l but this is not true if the initial PC is 48 × 10^9/l) [12]. In AIDS-free HIV+ cases, IR to IVIg is fast [33], ranging from 71% to 100% with a failure rate of 29% [13,21,34]. Previous reports described a few AIDS patients [21,23,26,27,35], and based on one patient it was suggested that lower response rates of HIV-Thr to IVIg would more likely be seen in AIDS compared to AIDS-free HIV+ individuals [26]. However, the utility of IVIg for HIV-Thr has not been addressed directly in AIDS. We excluded those conditions that could mask the response to IVIg: bone marrow infiltration or hypoplasia and peripheral nonimmune thrombocytopenia. As reported previously, we found myelodysplastic changes [36]; however, megakaryocyte counts were normal or high and the IR achieved further supports the absence of a true myelodysplastic syndrome. Our results show that low-dose IVIg is effective for HIV-Thr of AIDS. We found a 100% IR rate at the beginning of treatment sustained during five weeks and by the end of the protocol, the IR rate was 77%. Despite one study using periodic infusions as a maintenance therapy [19], LTR were not found after suspending IVIg [12,13]; however, we achieved a 38% LTR rate.

The pathogenesis of HIV-Thr includes decreased marrow platelet production [37] and immune platelet destruction [38]. Marrow insufficiency explains HIV-Thr of AIDS, whereas immune-mediated platelet destruction has a major role in HIV-Thr of AIDS-free HIV+ cases [13]. From this point of view, our failures in IVIg suggest bone marrow failure as the etiology of HIV-Thr. However, the fast and high IR rates, the effect on two bleeding patients promptly after starting IVIg, and the four LTRs, suggest an immune mechanism. On the other hand, Fc blockade explains the immediate effects of IVIg on the PC although other mechanisms have been proposed for long-term effects such as release of thrombopoietic cytokines from the reticuloendothelial system, enhancement of the antiidiotype antibody and T-cell suppressor function [39–41], etc. Our IR rate supports the Fc-mediated platelet clearance model suggesting that, at least partially, the reticuloendothelial system is intact [42] despite previous reports showing defective Fc receptor-mediated clearance [43,44]. Based on our results and in accordance with others [45], we believe that HIV-

Thr of AIDS is a complex mixture of marrow failure and autoimmune mechanisms acting simultaneously at different intensities.

Apparently, the pathophysiology of HIV-Thr differs among the several HIV risk groups [46,47]; however, there is no evidence of such differences in AIDS. This study only included adult homosexual male patients (>58% of HIV+ cases in our country belong to this risk group [48]). The beneficial effect of low-dose IVIg may be extended to cases of all HIV risk groups because in AIDS-free HIV+ individuals the response to HIV-Thr is independent of the risk group [12].

Economically, our results are encouraging because the major concern about IVIg is its high cost. Initially, high doses of IVIg for HIV-Thr were successfully used in five- or two-day courses [24,29,34]. Because the half life of IVIg preparations range from 15 to 58 days [49,50], we thought that weekly infusions might maintain adequate plasma levels of Ig. IVIg is effective as a long-term approach to avoid the risk of hemorrhage and also to delay splenectomy [51]. Thus, we hypothesize that once IR is achieved, a weekly low-dose IVIg maintenance regimen may sustain the response without high expenditure.

Long-term effects of IVIg in HIV+ cases are unknown. Using IVIg in the supportive care of children with non-thrombocytopenic AIDS, immunosuppression is not seen [52], and in Ig deficient cases, it reduces the infection rate [26]. Despite reports associating infection with IVIg [53], blockade of the Fc receptor function in ITP, and in vitro changes in Ig production, circulating lymphocytes, and T4:T8 ratio [54–56], it seems that IVIg is a safe approach for HIV-Thr of AIDS. We did not observe infections in a 169 week/patient period; however, this is a short follow-up to postulate any hypothetical benefit of IVIg on the immune status in AIDS.

This is the first report about the treatment of HIV-Thr using a low-dose IVIg. If the effect of IVIg on HIV-Thr and the hypothetical long-term maintenance with weekly infusions are validated in other studies, IVIg may be the first choice for this disorder in AIDS, thereby avoiding splenectomy. Meanwhile, IVIg may be indicated in thrombocytopenic AIDS patients in case of acute bleeding, or to prophylactically increase the PC either when a risk of hemorrhage exists but steroids are ineffective or contraindicated, or before emergency surgery or splenectomy when the general performance of the patient allows this surgical procedure without postoperative complications. IVIg cost may be handled better with this low-dose regimen and its advantages could be likely extended to AIDS-free HIV+ cases with HIV-Thr. Lastly, IVIg may have some role in the long-term infectious prophylaxis of AIDS, a highly desirable effect that should be studied further.

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